REMARKS

Claims 161-162, 261-262, and 280 are pending in this application for the Examiner's review and consideration. New claim 280 is merely the reintroduction of claim 165. Claims 166, 264-265, and 269 have been cancelled without prejudice. Applicants fully reserve their rights to prosecute the subject matter of any cancelled claim in one or more continuation, continuation-in-part, or divisional applications. Applicants have amended claims 161 and 162 as suggested by Examiner Celia Chang during the interview on April 5, 2006. As suggested, applicants added the d-spacing values for the 2θ values of the powdered x-ray diffraction as calculated using the Bragg equation ($n\lambda = 2d \sin\theta$). The value of λ was 0.00117. It is understood that the d-spacing values are entitled to the same range as the 2-theta values because the d-spacing values are calculated from the 2-theta values. No new matter has been added by this mathematical calculation.

Applicants note that the examiner inexplicably withdrew the allowance of claims 162 and 261 after noting that the claims were in condition of allowance in the Office Action dated June 28, 2005. Again, Applicants also note that the examiner inexplicably withdrew the allowance of claims 161, 162, 261, 262, 264, 265, and 269 after noting that the claims were in condition of allowance in the Office Action dated October 8, 2004. Despite repeated requests by Applicants, the Office Action has not provided any explanation for the withdrawal nor can one discern from the prosecution any reason as to why these claims were no longer allowable.

Applicants' appreciate the courtesies extended to their representatives, Patrick Birde, Reg. No. 29,770, King Lit Wong, Reg. No. 37,500, and Payam Moradian, Reg. No. 52,048, and to Galit Gonen-Cohen, Judith Aronhime, and Guatam R. Desiraju during the interview with Examiner Celia Chang conducted on April 5, 2006. The substance of the interview and the reasons presented at the interview as warranting favorable action are included in the comments below. As requested by Examiner Celia Chang, applicants submit a declaration under 37 C.F.R. § 1.132 by Guatam Desiraju. In this declaration, applicants explain that the crystalline zolpidem hemitartrate Form D characterized by five (5) PXRD peaks is distinct from other crystalline forms of zolpidem hemitartrate. Applicants also explain in the a declaration under 37 C.F.R. § 1.132 by Judith Aronhime that the crystalline form may contain water or ethanol within the crystal lattice or on the surface of the crystal and

that the water or ethanol either alone or in combination with the zolpidem hemitartrate do not create a reflection in the PXRD.

Applicants respectfully request the withdrawal of the finality of the Office Action. The prior Office Action rejected claims 264, 265, and 269 under 35 U.S.C. § 112, second paragraph for lack of antecedent basis. The present Office Action rejected claims other than 264, 265, and 269 for lack of definiteness and not on the same grounds for lack of antecedent basis. The rejection of claims 161-162, 166, 261 and 262 under § 112, second paragraph is new and not the result of any amendment made by the applicant. Thus, the finality of the Office Action should be removed.

Claims 161-162, 166, 261-262, 264-265, and 269 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite for the reasons set forth on pages 2 and 3 of the Office Action. Claims 166, 264-265, and 269 have been cancelled; however, as to the remaining claims, applicants respectfully traverse.

§ 112, second paragraph, states: "[t]he specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." 35 U.S.C. § 112, second paragraph (2006). Determining whether a claim is definite as required by § 112, second paragraph, requires an analysis of whether one skilled in the art would understand the bounds of the claim when read in light of the specification. *Solomon v. Kimberly-Clark Corp.* 216 F.3d 1372, 55 U.S.P.Q.2d 1279 (Fed. Cir. 2000) citing *Personalized Media Communications, LLC v. ITC*, 161 F.3d 696, 705, 48 U.S.P.Q.2d 1180, 1888 (Fed. Cir. 1998) (emphasis added). If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more. *Id.*

The Office Action states: "[i]t is very confusing as to what is the scope of the claims. Please note that one category of patentable invention is a 'product.'" Thereafter, the Office Action goes on to describe polymorphs. However, absent from the Office Action is any legal or factual ground as to why the skilled artisan would not understand the claims.

The claims have been amended as suggested by examiner Celia Chang during the interview of April 5, 2006 to overcome the rejection under § 112, second paragraph. As suggested, the claims were amended to recite the d-spacing values for the PXRD peaks.

Claim 161, as amended, recites: zolpidem hemitartrate Form D characterized by an X-ray powder diffraction pattern having peaks at about 7.1, 9.5, 14.1, 19.6 and 24.5 ± 0.2 degrees two-theta, and the corresponding d-spacing values of about 12.5, 9.3, 6.3, 4.53, and 3.63 Å. The specification discloses crystal forms of zolpidem hemitartrate as distinguished by X-ray diffraction spectroscopy and the equipment and methods used to obtain **all** powder x-ray diffraction patterns. (Application p. 8, ll. 28-30 and p. 9, l. 31 to p. 10, l. 3, emphasis added). With this information in hand, one of one of ordinary skill in the art can readily ascertain what is and what is not covered by claim 161 and claims dependent thereon. Thus, the claims are definite as to the recited zolpidem hemitartrate.

Applicants further submit that the recitation of five (5) PXRD peaks to identify zolpidem hemitartrate Form D is sufficient to characterize the crystalline form from other forms of zolpidem hemitartrate. Applicants offer the declaration of Professor Guatam R. Desiraju of the University of Hyderabad in support of the definiteness of the claim. Prof. Desiraju compares the PXRD pattern of zolpidem hemitartrate Form D and each of the other disclosed forms of zolpidem hemitartrate. The analysis by Prof. Desiraju conclusively demonstrates that the PXRD pattern of claim 161 defines one and only one crystalline form of zolpidem hemitartrate. No other crystalline form of zolpidem hemitartrate shares all five (5) peaks characterizing zolpidem hemitartrate Form D and as recited in claim 161. Thus, a skilled artisan performing the same analysis can determine easily whether their zolpidem hemitartrate is within the scope of the claim. Prof. Desiraju further explains that the likelihood that another crystalline form of zolpidem hemitartrate is characterized by the same five (5) peak pattern recited in claim 161 is minimal. Based on his experience, Prof. Desiraju calculated that the mathematical possibility that a second zolpidem hemitartrate crystalline form be the same as Form D to be 0.05% or about 1:2000. Thus, Prof. Desiraju established the uniqueness of zolpidem hemitartrate Form D over the other known forms of zolpidem hemitartrate.

In fact, the number of peaks sufficient to differentiate one crystalline form is dependent on the chemical compound and may require as few as one peak. For example, Yokoyama, *et al.*, were able to distinguish two polymorphic forms of benoxaprofen, forms I and II, using a single peak in the x-ray diffractogram. Yokoyama, *et al.*, *Chem. Pharm. Bull.*, 34(2) 917-921 (1986).

Moreover, the Federal Circuit has ruled that the named of crystalline material is sufficiently defined to satisfy the requirements of § 112, second paragraph. The Federal Circuit held definite a claim reciting "crystalline paroxetine hydrochloride hemihydrate" and stated that it was "not ambiguous but rather describes a specific compound." *Smithkline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1339 (Fed. Cir. 2005). Similarly, a claim reciting "zolpidem hemitartrate Form D" as characterized by five peaks of the x-ray diffractogram should equally found to be definite.

Accordingly, for the reasons discussed above, the rejection of claims 161-162 and 261-262 under 35 U.S.C. § 112, second paragraph, for being indefinite cannot stand and should be withdrawn.

Claim 166 stands rejected under 35 U.S.C. § 102(b) as allegedly anticipated by U.S. patent No. 5,891,891 to E. Benincasa ("the '891 patent") for the reasons set forth at pages 3-4 of the Office Action. Claim 166 has been cancelled and thus the rejection is now moot.

Claims 161, 166, 262, 264-265, and 269 stand rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious over U.S. patent Nos. 6,281,360 ("the '360 patent") to Ettema in view of 6,242,460 ("the '460 patent") and further in view of H.G. Brittain "Polymorphism in Pharmaceutical Solids," (Marcel Dekker Inc, NY 1999) ("the Britain reference") for the reasons set forth on pages 4-5 of the Office Action. Claims 166, 264-265, and 269 have been cancelled, as to the remaining claims applicants respectfully traverse.

"Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issued are to be ascertained; and the level of ordinary skill in the pertinent art resolved." *Graham v. John Deere*, 383 U.S. 1, (1966); *M.P.E.P.* 2141. The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that claimed subject matter could be carried out and would have a reasonable likelihood of success. *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988); *M.P.E.P.* 2143.02. As the Examiner is well aware, in order to form a proper basis for a rejection under 35 U.S.C. § 103, the prior art must provide some suggestion, either explicit or implicit, of the combination that allegedly renders a claimed invention obvious. *M.P.E.P.*, § 2142 (June 1998), *see also, Panduit Corp. v. Denisson Manufacturing Co.*, 1 U.S.P.Q.2d 1593, 1597 (Fed. Cir. 1987).

The Examiner can satisfy the burden of showing obviousness of the combination only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references. *In re Sang Su Lee*, 277 F.3d 1338, 1343, 61 U.S.P.Q.2d 1430 (Fed. Cir. 2002); citing *In re Fritch*, 972 F.2d 1260, 1265, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992). The need for specificity is paramount, particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected the components for combination in the manner claimed. *Id.* When the PTO seeks to rely upon a chemical theory, in establishing a *prima facie* case of obviousness, it must provide evidentiary support for the existence and meaning of that theory. *In re Grose*, 592 F.2d 1161, 1168-1169 (C.C.P.A. 1979); citing *In re Mills*, 281 F.2d 218, 223-224, (C.C.P.A. 1960); *M.P.E.P.* 2144.02. The Examiner's conclusory statements do not adequately address the issue of motivation to combine; the factual question of motivation is material to patentability, and can not be resolved on subjective belief and unknown authority. *In re Sang Su Lee*, 227 F.3d at 1343.

The '360 patent discloses the synthesis of imidazopyridine compounds of formula (I) among which is zolpidem, which when isolated or recovered by conventional means are generally at least 98% pure and usually more than 99% pure, **without the need to carry out subsequent purification** or the use of special purification/isolation techniques such as HPLC. (The '360 patent, col. 8, ll. 11-16) (emphasis added). Crystallization is **normally not necessary and it typically only employed for characterization purposes**. (*Id.* at ll. 61-67) (emphasis added). Example 6 crystallized zolpidem hemitartrate from methanol. (*Id.* col. 10, ll. 61-65).

The '460 patent discloses solid-phase zolpidem salt forms that exhibit improved physical stability over zolpidem hemitartrate. (The '460 patent, col. 3, ll. 61-62). The '460 patent states that "studies conducted by the present inventors have revealed that **forming the zolpidem tartrate [zolpidem hemitartrate] salt is difficult**." (*Id.* col. 1, ll. 34.36 and col. 2, ll. 5-6) (emphasis added). The '460 patent attested to the difficulty of making zolpidem tartrate by crystallizing a mixed solution of zolpidem free base and tartaric acid (2:1 molar ratio) in methanol: "[t]he present inventors repeated this method with the aim to test the ruggedness of production method in modeling situations encountered on an industrial scale (changes in temperature regimen, concentration of components, quality of solvent used, etc.) and

found out that the crystallization process is highly irreproducible." (*Id.* ll. 8-16, emphasis added). Trying to prepare zolpidem tartrate by crystallization using a 2:1 molar ratio of zolpidem and tartaric acid, and employing non-methanolic solvents such as ethanol, isopropanol, and acetone, results in no zolpidem tartrate; instead only zolpidem hydrogentartrate [zolpidem to tartaric acid molar ratio of 1:1] is obtained. (*Id.* col. 5, ll. 22-27 and col. 6, ll. 24-26).

The Brittain reference generally discloses polymorphs, and that most drug substances are obtained as microcrystalline powders, from which it is often difficult to obtain crystallographically adequate crystals. (The Brittain reference, p. 235). Yet, even the Brittain reference recognizes the difficulty in predicting polymorphs: "...the developmental scientist is handicapped in attempting to predict how many solid forms of a drug are likely to be found." (*Id.*, p. 185).

The Office Action has readily admitted that neither reference teaches nor suggests the 5 peaks in the X-ray diffraction pattern in claim 161, or the DTG thermogram of instant claim 262. See, Office Action of June 28, 2005, p. 4.

The '360 patent fails to render the present claims obvious, because the '360 patent fails to suggests or disclose zolpidem hemitartrate Form D. The '360 reference only generally discloses the synthesis of zolpidem hemitartrate, but does not disclose zolpidem hemitartrate characterized by the recited PXRD peaks. Moreover, the '360 patent teaches against making any particular zolpidem hemitartrate polymorph by discouraging crystallization and using crystallization for characterization purposes only.

To remedy the deficiencies of the '360 patent, the Office Action uses the '460 patent. Like the '360 patent, the '460 patent does not disclose or suggest zolpidem hemitartrate characterized by the recited PXRD peaks. In fact, contrary to the Office Action, the '460 patent teaches against the formation of zolpidem hemitartrate. The '460 patent disclosed the difficulty in reproducibly making the salt and their own failures in making the salt despite changing temperature, concentration, and quality of solvent, among others. Further, the '460 patent states that zolpidem hemitartrate has low physical stability, which can lead to unintended changes during manufacture or storage.

The proposed combination of the '460 patent and the '360 patent is contrary to the teachings in each reference. Example 6 of the '360 patent combines zolpidem (2 eq.) and tartaric acid (1 eq.) in **methanol**. Methanol is the solvent the '460 patent

explicitly discourages from use. Yet the Office Action proposes that the skilled artisan after reading the '460 patent (discouraging the use of methanol or the formation of zolpidem hemitartrate) would proceed to use methanol in the combination to obtain a stable zolpidem hemitartrate. Not only is there no suggestion or motivation to make the proposed modification, there is no reasonable expectation of success in doing so.

The proposed combination of the references is only possible using hindsight analysis. The suggested combination would require a substantial reconstruction and redesign of the elements shown in the '460 patent as well as a change in the basic principle under which the '460 patent was designed to operate. Basically, without any teaching or suggestion, the skilled artisan must change the solvent used in the '460 patent to methanol and ignore the specific teachings of zolpidem hemitartrate instability. However, as discussed above, the '460 patent explicitly teaches against such modifications.

In fact, the literature is replete with references attesting to the unpredictability of polymorphs. "The *possibility* of polymorphism may exist for any particular compound, but the conditions required to prepare as yet unknown polymorphs are by no means obvious." J. Bernstein, "Polymorphism in Molecular Crystals," p. 9 (Clarendon Press, Oxford 2002). This view has not changed over time. "Perhaps the chief challenge in managing the phenomenon of multiple solid forms of drug is our inability to predict how many forms can be expected in any given case." Byrn, *et al.*, "Solid-State Pharmaceutical Chemistry," *Chem. Mater.* 6, 1148-1158 (1994). For example, only recently was a second polymorph for aspirin found despite being first synthesized in 1853. Wishweshwar, *et al.*, *J. Am. Chem. Soc.*, 127, 16802-16803 (2005). The process of crystallization is affected by many physical parameters, and this element of predictability has serious implications for solids design in crystal engineering. M. Caira, (Crystalline Polymorphism of Organic Compounds," *Topics in Current Chemistry*, vol. 198, 164-208 (1998). "There's no way to tell what a large floppy molecule can do in the solid state except by doing experiments." M. Rouhi, "The Right Stuff," Chem. & Eng. News 32-35 (2003). "Until that time [that computer programs are able to predict stable crystal forms] the development scientist is handicapped in attempting to predict how many solid forms of a drug are likely to be found." H.G. Brittain, "Polymorphism in Pharmaceutical Solids," p. 185 (Marcel Dekker 1999).

Yet, with no specific citation, the Office Action proposes that polymorphs are predictable by stating that "it is well recognized in the pharmaceutical art that multiple forms may occur in drugs which will give different X-ray pattern [sic] but not all of them are polymorphs (see US pharmacopia)." The Office Action further states "[i]n addition, X-ray diffraction pattern [sic] are identification of 'crystals' i.e. physical forms, it does not provide information of the chemical nature." As repeated during the interview, the Office Action maintains that polymorphs are known and that they can be "picked" by the skilled artisan. Applicants have reiterated the unpredictability of making and characterizing selecting zolpidem hemitartrate Form D. If the Office Action continues to maintain that polymorphs are known and that based on this knowledge the skilled artisan can pick zolpidem hemitartrate Form D, **applicants request an affidavit or declaration by the examiner setting forth the specific factual statements and explanations** to support such a finding. See M.P.E.P 2144.04 and 37 C.F.R. 1.104(d)(2).

Yet, even combining all cited references, the combination does not render the claims obvious. The Brittain reference is merely a general reference that discloses polymorphs. The Board of Patent Appeals and Interferences repeatedly has rejected repeatedly obvious determinations based upon the combination of a specific reference that discloses a compound and a general reference about polymorphs. Although the following cases were not written for publication, applicants offer them for the reasoning and conclusions therein. In each case the Board refused to find obviousness when an examiner coupled a reference of a compound with a general teaching. *Ex parte Havens*, 2003 WL 21279863 (B.P.A.I. 2003) ("[t]he examiner's obviousness rejection seems to suffer from the same infirmity as her anticipation rejection, namely that it is directed to delavirdine mesylate per se, rather than to the specific S and T crystal forms of delavirdine mesylate that are the subject of the claims on appeal); *Ex parte Polniaszek*, 2003 WL 22282265 (B.P.A.I. 2003) ("...notwithstanding that the claimed compound has the same formula as Murugesan, the examiner has not established that Murugesan suggests appellants' specific claimed polymorph."); *Ex parte Meisel*, 2002 WL 32334598 (B.P.A.I. 2002) ("Dieter, while teaching the compound that is the subject of the claims is known, does not teach or suggest that the compound has different crystalline structures."); and *Ex parte Gala*, 2002 WL 851814 (B.P.A.I. 2002) ("According to the examiner, polymorph form 2 loratidine is merely another form of an old product (polymorph form 1 loratidine) and both forms possess

the same utility. Accordingly, the examiner concludes that applicants' claims, reciting polymorph form 2 loratidine, are unpatentable. **We disagree**. We invite attention to *In re Cofer*, ... where the court **substantially discredited PTO reliance** on the above-quoted proposition of law...") (emphasis added). In fact, *Ex parte Gala*, overturned a rejection under § 103 from an examiner in the 1625 group, the group of the present examiner. A copy of each case is attached to this amendment for the Examiner's convenience.

During the interview, examiner Celia Chang requested a demonstration of unexpected advantages. Applicants do not agree that the examiner has presented a *prima facie* case of obviousness, especially in view of the decisions by the Board of Patent Appeals and Interferences. However, to expedite prosecution and demonstrate the uniqueness of the recited crystalline form of zolpidem hemitartrate Form D, applicants present the declaration by Judith Aronhime regarding unexpected results.

In her declaration, Judith Aronhime demonstrates that zolpidem hemitartrate Form D is stable after formulation and is not hygroscopic. The formulation study in the Aronhime declaration tested zolpidem hemitartrate Form D under formulation and tabletting conditions.

As the study demonstrated, the crystalline zolpidem hemitartrate Form D never changed into another form, Form D was stable during formulation and tabletting. This is of particular advantage, because during the pharmaceutical formulation process, significant mechanical stress is placed on the active ingredient. Processes such as milling and compression to produce a tablet may alter the crystalline form. To ensure consistency and uniformity, it is vital that the drug form chosen is stable under the manufacturing conditions. In fact, in the Aronhime declaration a formulation of zolpidem hemitartrate Form D was made and tested for crystalline stability. As shown, before and after formulation preparation the zolpidem hemitartrate did not change.

Water may degrade or catalyzed the degradation of a drug. A compound having low hygroscopicity is important because humid manufacturing or storage conditions may detrimentally affect the stability of a compound. The Aronhime declaration determined the hygroscopicity for each compound in accordance with the method described in the European Pharmacopoeia 5.02, chapter 5.11 (January 2005). A copy of the test is attached as an exhibit in the Aronhime declaration. Each sample was exposed to 80% relative humidity at 25°C for 24 hours. Afterwards, each sample

was weighed to determine the weight of the water absorbed. Form A was found to absorb 0.02 g of water or 0.4% by weight. In contrast, Form D did not absorb water under the test conditions. Thus, Form A absorbs water while Form D does not.

Therefore, the crystalline zolpidem hemitartrate Form D has unexpected stability advantages over the prior art Form A. Form D does not alter form during formulation and does not absorb water. Both qualities are important during formulation and manufacture of the drug.

Accordingly, the rejection of claims 161 and 262 under 35 U.S.C. § 103(a) as rendered obvious by the '360 patent in view of the '460 patent and further in view of the Brittain reference cannot stand and should be withdrawn.

Applicants note that because the rejection of claims 161, 166, 262, 264-265, and 269 under 35 U.S.C. § 103(a) over the '891 patent in view of U.S. patent No. 4,382,938 ("the '938 patent") to Kaplan and Wall, "Pharmaceutical Application of Drug Crystal Studies," ("the Wall reference") and further in view of the Britain reference was not repeated; thus, this rejection must have been overcome.

Accordingly, it is believed that claims 161-162, 261-262, and 280 are now in condition for allowance, early notice of which would be appreciated.

If any outstanding issues remain, the examiner is invited to telephone the undersigned at the telephone number indicated below to discuss the same. No fee is believed to be due for the submission of this response. Should any fees be required, please charge such fees to Kenyon & Kenyon, LLP Deposit Account No. 11-0600.

Respectfully submitted,

Dated: 5/25/06

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